THE PHILIPPINE
JOURNAL OF SCIENCE
B. TROPICAL MEDICINE
VOL. XII SEPTEMBER, 1917 No. 5

A SURVEY OF CERTAIN CHEMICALS WITH REGARD TO THEIR BACTERICIDAL ACTION ON CHOLERA VIBRIOS WITHIN THE BODY OF EXPERIMENTAL CHOLERA CARRIERS [1]

By OTTO SCHÖBL

(From the Serum Section of the Biological Laboratory, Bureau of Science, Manila, and the Quarantine Laboratory, Health Officers' Department, Port of New York)

An experimental study of the bactericidal action of drugs upon cholera vibrios in the animal body is of considerable interest. It presents a rational method of searching for a remedy for the cure of cholera carriers and offers a method of testing the value of the so-called intestinal antiseptics.

Previously published studies on experimental cholera carriers brought to light the following facts. Direct inoculation of cholera culture into the gall bladder is the safest method of producing the state of cholera carriers in experimental animals.(1) A comparatively small amount of cholera culture, injected into the gall bladder, may suffice to produce this condition in animals.(2) The virulence of the cholera culture increases by being passed from one carrier to another.(3) The condition in question is an inflammation,(4) more or less pronounced, of the gall bladder, which under certain circumstances may extend to the liver. No evidence was found to indicate that the infection would extend further so as to assume the septicæmic type. Once the cholera vibrios establish themselves in the gall passages, the bile offering favorable conditions, they multiply therein and are being discharged into the small intestine, where they remain practically without competition. In the large intestine, due to the presence of numerous other bacteria, the

[1] Received for publication May 26, 1917.

cholera vibrios are not found as regularly as they are in the proximal part of the intestine. They are rarely excreted in the fæces, unless the sojourn of the intestinal contents is hastened through the large intestine and the conditions are made favorable to the survival of the cholera vibrios.(4, 5)

From these findings it is evident at once that the problem of drug treatment in experimental cholera carriers is one of great difficulty. Even a drug which, given by mouth, would exert bactericidal action upon the cholera vibrios in the intestine would not bring about a complete and permanent disappearance of cholera vibrios from the body organism unless it was eliminated through the bile in such a chemical form as to be toxic to the cholera vibrios in a higher degree than it is deleterious to the body organism.

Guinea pigs were selected for these experiments for several reasons. It has been found and already mentioned in a previous paper that the inflammation of the gall bladder, following the intravesicular injection of cholera culture, is far more intense in rabbits than in guinea pigs.(3) It was to be expected, therefore, that the effect of a drug would be evident in case of a slight infection, more so than in a case of a severe one. Furthermore, in previous experiments on six rabbits, which were found positive in from three to thirteen days after the infection, four harbored the cholera vibrios in the gall bladder only(3) and not in the intestine. Should rabbits be used for treatment experiments, it would be difficult at times to say whether or not the disappearance of cholera vibrios from the intestine, in itself a therapeutic result of value, is due to the action of the drug. Besides these considerations it was found technically more convenient and more economic to use guinea pigs.

THE ARRANGEMENT OF EXPERIMENTS

Infection.—The intravesicular injection was used exclusively in these experiments. A recently isolated culture of cholera was grown in ox bile and transplanted in agar twenty-four hours before the injection was performed. The animals were shaved, and the skin was washed with lysol solution and then painted with tincture of iodine. In performing the operation, an incision was made from the middle of the xiphoid process to the right costal margin. As soon as the muscles were separated, the peritoneum became visible and through it the xiphoid process. The latter was clasped with a hemostat and lifted up, whereupon the duplicature of the peritoneum formed thereby was perforated by means of a dull forceps. As a rule, the gall bladder was

immediately visible, and prolapsing into the laparotomy wound, it closed the opening, thus preventing exposure of the other organs. Therefore the injection could be made outside the peritoneal cavity. Only fractions of a cubic centimeter were injected into the gall bladder. The inoculation finished, the puncture in the gall bladder was closed with a ligature, the ends of the wound were lifted up, and the gall bladder assumed its normal position. Threads thoroughly soaked with tincture of iodine were used for suturing the abdominal wound.

Examination.—To ascertain the effect of the drug, the animals were killed and examined within several hours after the last administration of the drug. The shaved skin over the chest and abdomen was wetted with 2 per cent lysol solution. The abdomen and thorax were opened separately. The gall bladder, the proximal part of the intestine (in the reports, duodenum), the distal part of the small intestine (in the reports, the ileum), and the cæcum were removed from the abdomen—first the gall bladder, then the duodenum, ileum, cæcum, in order, a separate set of sterilized instruments being used for each organ. The gall bladder was taken out in toto, including a portion of the bile duct. The contents of the gall bladder were emptied into peptone water, and the gall bladder, together with the bile duct, was placed in a culture tube. The contents of the proximal part of the small gut were planted, and the intestine, cut into small pieces, was added to the same peptone tube. At least one half of the distal part of the small intestine was planted in the same way as the duodenum. Five large loopfuls of the contents of the cæcum were inoculated into peptone water. One loopful of the contents of the various organs mentioned above was plated directly on Dieudonné agar plates. After six hours of incubation second peptone cultures were planted from the first peptone tubes. At the end of twenty-four hours Dieudonné plates were made from the first and the second peptone cultures.

It was the purpose of these experiments to test as many chemicals as possible in the hope that some of them would show an indication of curative effect. For this reason comparatively few animals were treated with each drug, the intention being to extend the experiments later on, using those chemicals which showed promising results in the present investigations.

As to the dosage of the drugs small doses were given at the start. The quantity of the drug was gradually increased until toxic symptoms—even death—occurred as a consequence of the drug-feeding. It was intended to saturate the body organism of the animals with the particular drug. In order to see the imme-

diate effect of the drug upon the cholera vibrios, particularly in the intestine, the animals were killed within a few hours after the last feeding instead of awaiting the time when a complete elimination of the chemical from the animal body could be reasonably expected.

The objection to such a procedure, namely, the possibility of transferring into the culture medium an amount of the drug sufficient to inhibit the growth of cholera vibrios in the cultures, was kept in mind, but it soon became evident that this factor hardly warranted consideration. Numerous experiments with various chemicals were made in this way without any apparent curative effect of the drugs being noticeable. Furthermore the present investigation was intended for orientation only, and those drugs which showed any effect at all were to be further studied.

The results of our experiments are summarized in Tables I to VIII. From ten to twelve animals were inoculated and treated at the same time, one of the carriers, at least, being kept as a control. The administration of the drugs took place either by intramuscular injection or by mouth. For the latter way of drug application an inert oil was found technically more convenient than water. The animals under treatment were killed not later than the tenth day, provided they survived the treatment that long. It has been found in our previous experiments that a certain percentage of experimental cholera carriers become spontaneously negative after the thirteenth day. Therefore the duration of treatment had to be limited to ten days.

For the sake of convenience we have arranged the chemicals and drugs that were used in the present experiments into seven groups.

The first group contains simple organic compounds: Benzene, toluene, and xylene.

The second group contains halogen derivatives: Chloroform, bromoform, and chloral.

The third group represents phenols and related compounds: Salicylates, benzoic acid, resorcin, brenzkatechin, guaiacol, gallic acid, pyrogallol, carvacrol, thymol, creosote, xylenol, and alpha- and beta-naphthol.

The fourth group contains miscellaneous organic compounds, the majority of which are official in the pharmacopœia: Urotropin, Ol. caryophylli, Ol. cinamoni, Ol. copaibæ, camphor, eucalyptol, anethol, phenetol, terpineol, and turpentine.

Two alkaloids, namely, quinine and emetine, were tried also because of their usefulness in chemotherapy. (The fifth group.)

Certain representatives of the officinal compounds of metals

were placed in the sixth group. Magnesium peroxide, potassium iodide, potassium permanganate, calomel, mercury salicylate, antimony tartrate, antimony trioxide, arsenic trioxide, sodium cacodylate, atoxyl, 606 Ehrlich.

The seventh group comprises a few anilin dyes. It is known of some of these chemicals that they act in vitro as strong and selective antiseptics. The following dyes were tested: Methylene blue, gentian violet, brilliant green, fuchsin, trypan red and blue, scarlet red, chrysoidin, vesuvin, victoria blue, and crystal violet.

Judging the effect of drug treatment by the results of these experiments, one can see that none of the drugs tested showed such prompt effect as to bring complete sterilization of the animal's body organism in a short time in every case.

Nevertheless there are certain indications evident of the possibility of shortening the duration of the state of cholera carrier. The effect of drug treatment in our experiments appears to be of three degrees.

First degree.—The absence of cholera vibrios on the direct plates made from the intestine, indicating diminution of cholera vibrios in the intestinal tract. Findings of this type are considered of little importance, since physiologic conditions undoubtedly influence the variation in numbers of cholera vibrios in the intestine. Nevertheless, compared with the findings in untreated controls, the absence of cholera colonies on direct plates can be considered as an effect of drug treatment, and drugs effecting such findings deserve further attention.

Second degree.—Absence of cholera vibrios on direct plates as well as in peptone cultures both made from the intestine, indicating absence of cholera vibrios from the intestine at that time. Drugs showing this effect may reasonably be considered intestinal antiseptics of value, in as much as they bring about a disinfection of the intestine even if only temporarily.

Third degree.—Absence of cholera on all direct plates and in all peptone cultures, including those made from bile and from the gall bladder. Considering the ease with which cholera vibrios can be detected with the aid of a selective medium and particularly by employing the peptone enrichment process, one is bound to consider these findings as sufficient evidence of complete absence of cholera vibrios from the body organism.

In this group (Table I) only benzene showed a slight effect in as much as one out of three guinea pigs after ten days' treatment harbored so few cholera vibrios in the intestine that none grew on direct plates. Cholera vibrios, however, were detected by the enrichment process.

No curative effect was noticeable in these experiments (Table II). The majority of animals died as a consequence of the treatment. Autopsy revealed extensive degeneration of the internal organs, particularly of the liver.

The following chemicals showed an indication of curative effect (Table III):

1. Brenzkatechin. One animal treated with this chemical for nine days showed no cholera on direct plates, but cholera vibrios were present in peptone cultures.

2. Guaiacol. In three of four animals treated with guaiacol there was an effect noticeable. Twice cholera vibros were not found at all in the ileum, while in one case after nine days' treatment the cholera vibrios were absent from the entire alimentary tract.

3. Pyrogalol. First degree effect after nine days' treatment.

4. Carvacrol. Second degree effect in one animal treated eight days, no effect in one animal treated seven days. Both animals died.

In this group (Table IV) only turpentine showed a slight effect of the first degree, but the animal died in two days.

The following chemicals of this group showed an indication of a curative effect (Table VI):

1. Antimony trioxide. Curative effect of first degree in one animal after eight days' treatment. In another animal no effect was noticeable after four days' treatment.

2. Arsenic trioxide. This chemical, given in large doses, brought about death in two animals treated; in small doses after nine days' treatment by intramuscular injections, complete disappearance of cholera vibrios from the entire alimentary canal. Application by mouth of the same chemical for three days remained without effect in one case.

3. Atoxyl and sodium cacodylate showed effect of first degree after eight and nine days' treatment, respectively.

4. Ehrlich-Hata 606. Twelve experimental cholera carriers were treated by intramuscular injections of this drug. Four of them died. In four of the twelve the cholera vibrios have apparently disappeared completely during the treatment; in the other two the effect of the first degree was noticeable.

Of the dyes tested in these experiments (Table VII) only methylene blue deserves mention. It showed a first degree effect in one instance.

These experiments are by no means final; still they show that the problem of drug treatment of cholera carriers is not utterly hopeless. None of the chemicals gave such prompt curative effect as to bring about complete disappearance of cholera vibrios from the animal's body in every case. It is hardly probable that any such drug will be found. The drugs listed as phenol group and the arsenic compounds are of some promise. Since it is within our power to prolong the duration of the carrier state in animals by feeding bile,(5) it is hoped that drug-treatment experiments performed on bile-fed animals will allow a period of treatment extended beyond the ten days' limit and thus bring more definite results than those obtained in the present investigations. Combination treatment by several drugs suggests itself also.

REFERENCES

1. *Journ. Inf. Dis.* (1916), **18**, 307–314.
2. *Phil. Journ. Sci., Sec. B* (1916), **11**, 153–155.
3. *Journ. Inf. Dis.* (1916), **19**, 145–152.
4. *Phil. Journ. Sci., Sec. B* (1916), **11**, 157–158.
5. Ibid., *Sec. B* (1917), **12**, 23.

TABLE I.—*Showing the results of experiments with benzene, toluene, and xylene.*

[—, cholera vibrios not found; +, cholera vibrios present; v. n., more than 200; n., about 200; f., about 12; v. f., less than 6; o., not examined; p. o., per os; int., intramuscular; inj., injection.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Benzene	8	1.50	p. o.	Yes	No	10	v. n.	—	v. f.	v. f.	+	+	+	+
2	do	8	1.50	p. o.	Yes	No	10	f.	v. f.	v. f.	v. f.	+	+	+	+
3	do	10	3.25	p. o.	Yes	No	10	f.	—	—	—	+	+	+	+
1	Toluene	4	1.85	p. o.	Yes	No	5	o.	o.	o.	o.	+	+	+	+
2	do	5	1.05	p. o.	Yes	No	6	v. n.	f.	v. f.	—	+	+	+	+
3	do	8	1.50	p. o.	Yes	No	10	n.	f.	n.	f.	+	+	+	+
1	Xylene	3	1.60	p. o.	Yes	No	4	v. n.	n.	v. n.	f.	+	+	+	+
2	do	5	1.05	p. o.	Yes	No	6	v. n.	f.	n.	v. f.	+	+	+	+
3	do	8	1.50	p. o.	Yes	No	10	v. n.	v. f.	v. f.	—	+	+	+	+

TABLE II.— *Showing the results of experiments with chloroform, bromoform, and chloral.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Chloroform	2	0.20	p. o.	Yes	No	3	v. n.	v. n.	v. n.	+	+	+	+	+
2	do	3	0.30	p. o.	Yes	No	4	n.	—	n.	f.	+	+	+	+
3	do	3	0.30	p. o.	Yes	No	4	v. n.	v. n.	v. n.	f.	+	+	+	+
4	do	3	0.30	p. o.	Yes	No	6	o.	o.	o.	o.	+	+	+	−
1	Bromoform	3	0.10	p. o.	Yes	No	4	v. n.	v. n.	v. n.	−	+	+	+	−
2	do	5	0.15	p. o.	Yes	No	6	v. n.	v. n.	v. n.	n.	+	+	+	+
1	Chloral	6	0.34	p. o.	Yes	No	7	v. n.	v. n.	v. n.	n.	+	+	+	+
2	do	6	0.34	p. o.	Yes	No	7	v. n.	v. n.	n.	n.	+	+	+	+

TABLE III.—*Showing the results of experiments with phenols and closely related compounds.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Sodium salicylate	1	0.50	p. o.	Yes	No	2	o.	o.	o.	o.	+	+	+	+
2	do	7	0.80	p. o.	No	Yes	8	f.	v. f.	f.	f.	+	+	+	+
1	Salol	3	0.15	p. o.	No	Yes	13	o.	o.	o.	o.	+	+	+	+
2	do	9	1.50	p. o.	No	Yes	9	n.	f.	f.	f.	+	+	+	+
1	Methyl salicylate	3	1.50	p. o.	Yes	No	5	o.	o.	o.	o.	+	+	+	+
1	Salipyrin	6	1.50	p. o.	No	Yes	7	v. n.	v. f.	n.	f.	+	+	+	+
1	Benzoic acid	10	1.50	p. o.	No	Yes	10	n.	v. f.	f.	v. f.	+	+	+	+
1	Resorsin	8	0.52	p. o.	No	Yes	9	n.	n.	n.	n.	+	+	+	+
1	Brenzkatechin	3	0.15	p. o.	Yes	No	4	v. n.	v. n.	v. n.	v. n.	+	+	+	+
2	do	9	0.30	p. o.	Yes	No	10	f.	—	—	—	+	+	+	+
1	Guajacol	6	0.06	p. o.	No	Yes	7	f.	v. f.	—	—	+	+	—	—
2	do	7	1.13	p. o.	Yes	No	7	v. n.	v. n.	v. n.	—	+	+	+	—
3	do	9	1.50	p. o.	Yes	No	10	—	—	—	—	—	—	—	—
4	do	10	2.13	p. o.	Yes	No	10	f.	v. f.	—	—	+	+	—	—
1	Gallic acid	8	0.5	p. o.	Yes	No	9	v. n.	f.	n.	n.	+	+	+	+
1	Pyrogalol	8	0.5	p. o.	Yes	No	9	f.	—	—	—	+	+	+	—
1	Carvacrol	7	1.07	p. o.	Yes	No	7	v.	f.	n.	—	+	+	+	+
2	do	8	1.07	p. o.	Yes	No	8	—	—	—	—	+	+	+	+
1	Thymol	3	0.075	p. o.	No	Yes	13	o.	o.	o.	o.	+	+	+	+
2	do	3	0.30	p. o.	Yes	No	6	o.	o.	o.	o.	+	+	+	+
3	do	7	0.70	p. o.	Yes	No	9	v. n.	f.	v. f.	—	+	+	+	+
1	Creosote	4	0.04	p. o.	Yes	No	6	n.	n.	v. n.	f.	+	+	+	+
1	Cresotal	8	1.20	p. o.	Yes	No	10	v. n.	n.	f.	v. f.	+	+	+	+
1	Xylenol	5	0.95	p. o.	Yes	No	6	v. n.	v. n.	v. n.	n.	+	+	+	+

2	do	8	1.15	p. o.	Yes	No	9	v. n.	v. n.	v. n.	v. n.	+	+	+	+
1	Alphanaphthol	4	0.2	p. o.	Yes	No	7	n.	n.	n.	f.	+	+	+	+
1	Betanaphthol	3	0.30	p. o.	Yes	No	6	o.	o.	o.	o.	+	+	+	+
2	do	8	0.35	p. o.	No	Yes	9	v. n.	v. f.	f.	—	+	+	+	—
3	Betol	2	0.2	p. o.	Yes	No	3	o.	o.	o.	o.	+	+	+	+
4	do	3	0.3	p. o.	Yes	No	6	o.	o.	o.	o.	+	+	+	+

TABLE IV.—*Showing results of experiments with miscellaneous organic compounds.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Urotropin	3	1.25	p.o.	No	Yes	6	o.	o.	o.	o.	+	+	+	−
2	do	6	2.00	p.o.	No	Yes	8	o.	o.	o.	o.	+	+	+	+
3	do	8	9.00	p.o.	No	Yes	9	v. n.	n.	v. n.	−	+	+	+	+
1	Oleum caryophylli	4	0.57	p.o.	Yes	No	4	v. n.	v. n.	n.	v. f.	+	+	+	+
2	do	10	1.67	p.o.	No	Yes	10	v. n.	n.	−	−	+	+	+	−
1	Oleum cinamoni	5	0.59	p.o.	Yes	No	7	v. n.	f.	f.	−	+	+	+	+
1	Oleum copaibae	1	0.20	p.o.	No	Yes	3	o.	o.	o.	o.	+	+	+	+
2	do	3	1.50	p.o.	Yes	No	4	o.	o.	o.	o.	+	+	+	+
1	Camphor	3	0.30	p.o.	No	Yes	5	o.	o.	o.	o.	+	+	+	−
2	do	3	0.30	p.o.	No	Yes	4	n.	f.	v. n.	n.	+	+	+	+
1	Eucalyptol	5	1.40	p.o.	No	Yes	10	o.	o.	o.	o.	+	+	+	+
1	Anethol	5	0.50	p.o.	Yes	No	5	v. n.	v. n.	v. n.	v. n.	+	+	+	+
2	do	10	2.48	p.o.	No	Yes	10	v. n.	f.	n.	−	+	+	+	−
1	Phenethol	9	3.13	p.o.	No	Yes	9	v. n.	n.	v. n.	v. n.	+	+	+	+
2	do	9	3.13	p.o.	No	Yes	9	v. n.	v. n.	v. n.	n.	+	+	+	+
1	Terpineol	7	1.63	p.o.	Yes	No	7	v. n.	−	v. f.	−	+	+	+	+
2	do	9	2.63	p.o.	No	Yes	9	v. n.	n.	v. n.	f.	+	+	+	+
1	Terpentine	2	0.20	p.o.	Yes	No	3	f.	−	−	−	+	+	+	+

TABLE V.—*Showing the results of experiments with quinine and emetine.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Quinine sulphate	13	0.3	p. o.	No	Yes	13	o.	o.	o.	o.	+	+	+	+
2	Quinine hydrochlorate	4	0.4	p. o.	Yes	No	5	o.	o.	o.	o.	+	+	+	−
1	Emetine hydrochlorate	3	0.6	int.	Yes	No	3	o.	o.	o.	o.	+	+	+	+
2	do	2	0.5	int.	Yes	No	2	o.	o.	o.	o.	+	+	+	+

TABLE VI.—*Showing the results of experiments with inorganic compounds.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Magnesium peroxide	4	8.00	p. o.	No	Yes	6	v. n.	n.	v. n.	f.	+	+	+	+
2	do	7	3.50	p. o.	No	Yes	9	v. n.	f.	n.	—	+	+	+	+
1	Potassium iodide	1	0.50	p. o.	No	Yes	2	o.	o.	o.	o.	+	+	+	+
2	do	7	0.80	p. o.	No	Yes	8	v. n.	v. n.	v. n.	v. n.	+	+	+	+
1	Potassium permanganate	3	0.30	p. o.	No	Yes	17	o.	o.	o.	o.	+	+	+	+
2	do	3	0.30	p. o.	Yes	No	4	v. n.	n.	f.	v. f.	+	+	+	+
1	Calomel	1	0.10	p. o.	Yes	No	4	o.	o.	o.	o.	+	+	+	+
2	do	3	0.015	p. o.	Yes	No	4	v. n.	v. n.	v. n.	n.	+	+	+	+
3	do	6	0.045	p. o.	Yes	No	7	o.	o.	o.	o.	+	+	+	+
1	Mercury salicylate	3	0.02	p. o.	Yes	No	4	v. n.	v. n.	v. n.	f.	+	+	+	+
2	do	6	0.05	int.	No	Yes	8	o.	o.	o.	o.	+	+	+	+
1	Antimony tartarate	1	0.005	p. o.	Yes	No	2	n.	n.	n.	f.	+	+	+	+
2	do	1	0.005	p. o.	Yes	No	1	n.	n.	n.	f.	+	+	+	+
3	do	6	0.045	int.	No	Yes	6	n.	v. f.	n.	f.	+	+	—	+
1	Antimony trioxide	4	0.056	int.	No	Yes	6	v. n.	n.	v. n.	n.	+	+	+	+
2	do	8	0.056	int.	No	Yes	10	n.	—	—	—	+	+	+	—
1	Arsenic trioxide	1	0.005	int.	Yes	No	2	n.	n.	—	—	+	+	+	—
2	do	1	0.005	int.	Yes	No	2	f.	v. f.	f.	—	+	+	+	—
3	do	3	0.004	p. o.	No	Yes	6	n.	f.	f.	v. f.	+	+	+	—
4	do	9	0.0035	int.	No	Yes	10	—	—	—	—	—	—	—	—
1	Sodium cacodylate	9	1.364	int.	No	Yes	10	v. f.	—	—	—	+	+	+	+
1	Atoxyl	8	1.34	int.	No	Yes	10	v. n.	v. f.	—	—	+	+	+	+
1	Ehrlich 606	1 inj.	0.005	int.	Yes	No	6	n.	n.	n.	f.	+	+	+	+
2	do	1 inj.	0.020	int.	Yes	No	6	n.	n.	n.	n.	+	+	+	+

3	do	1 inj.	0.020	int.	Yes	No	5	v. n.	f.	v. n.	—	+	+	+	—
4	do	2 inj.	0.010	int.	No	Yes	9	v. f.	—	f.	v. f.	+	+	+	+
5	do	2 inj.	0.020	int.	No	Yes	9	f.	v. f.	f.	—	+	+	+	+
6	do	3 inj.	0.035	int.	No	Yes	3	—	—	—	—	—	—	—	—
7	do	3 inj.	0.015	int.	No	Yes	4	—	—	—	—	—	—	—	—
8	do	4 inj.	0.085	int.	Yes	No	5	—	—	—	—	—	—	—	—
9	do	6 inj.	0.020	int.	No	Yes	7	—	—	—	—	—	—	—	—
10	do	5 inj.	0.065	int.	No	Yes	10	n.	v. f.	—	—	+	+	+	+
11	do	4 inj.	0.045	int.	No	Yes	10	n.	—	—	—	+	+	+	+
12	do	4 inj.	0.065	int.	No	Yes	10	v. n.	n.	v. n.	f.	+	+	+	+

TABLE VII.—*Showing the results of experiments with certain anilin dyes.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Duration.	Total amount of drug.	Administered.	Sick.	Well.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
								Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
		Days.	*g.*												
1	Methylene blue	3	0.025	p.o.	No	Yes	10	o.	o.	o.	o.	+	—	—	—
2	do	3	0.093	p.o.	No	Yes	6	o.	o.	o.	o.	+	+	+	+
3	do	4	0.093	p.o.	No	Yes	6	o.	o.	o.	o.	+	+	+	+
4	do	5	0.025	p.o.	No	Yes	6	o.	o.	o.	o.	+	+	+	+
1	Gentian violet	3	0.025	p.o.	No	Yes	10	o.	o.	o.	o.	+	+	+	+
1	Brillant green	3	0.025	p.o.	Yes	No	10	o.	o.	o.	o.	+	+	+	+
1	Fuchsin	1	0.10	p.o.	Yes	No	2	n.	n.	n.	n.	+	+	+	+
2	do	3	0.30	p.o.	Yes	No	4	o.	o.	o.	o.	+	+	+	+
3	do	3	0.012	p.o.	Yes	No	6	o.	o.	o.	o.	+	+	+	+
1	Trypan red	7	2.25	p.o.	No	Yes	7	n.	+	f.	v.f.	+	+	+	+
1	Trypan blue	7	3.50	p.o.	No	Yes	7	n.	—	n.	—	+	+	+	+
1	Scarlet red	6	0.60	p.o.	Yes	No	7	v. n.	v. n.	v. n.	f.	+	+	+	+
1	Chrysoidin	7	0.70	p.o.	Yes	No	8	v. n.	n.	n.	f.	+	+	—	+
1	Vesuvin	7	0.70	p.o.	Yes	No	8	v. n.	n.	n.	n.	+	+	+	+
1	Victoria blue	2	0.10	p.o.	Yes	No	2	v. n.	n.	n.	n.	+	+	+	+
1	Crystal violet	2	0.20	p.o.	Yes	No	3	v. n.	n.	n.	f.	+	+	+	+

TABLE VIII.—*Showing untreated controls.*

[See Table I for abbreviations and signs.]

Animal No.	Drug.	Autopsy, days after infection.	Direct plates.				Peptone cultures.			
			Bile.	Duodenum.	Ileum.	Cæcum.	Gall bladder.	Duodenum.	Ileum.	Cæcum.
1	Control	4	n.	f.	n.	v. f.	+	+	+	+
2	do	5	v. n.	v. n.	n.	f.	+	+	+	+
3	do	6	v. n.	n.	v. n.	n.	+	+	+	+
4	do	6	v. n.	f.	n.	f.	+	+	+	+
5	do	6	v. n.	n.	n.	—	+	+	+	—
6	do	7	v. n.	v. n.	n.	v. f.	+	+	+	+
7	do	7	v. n.	f.	v. n.	v. f.	+	+	+	+
8	do	9	n.	v. f.	f.	—	+	+	+	+
9	do	10	v. n.	n.	f.	—	+	+	+	—
10	do	10	n.	—	f.	—	+	+	+	—
11	do	10	n.	—	n.	—	+	+	+	—
12	do	10	v. n.	n.	v. n.	n.	+	+	+	+
13	do	11	v. n.	f.	f.	—	+	+	+	+

INCIDENCE OF AGE, ATHEROMA, AND ANEURISMS AS SEEN IN AUTOPSIES OF FILIPINOS [1]

By C. H. MANLOVE

(From the Department of Pathology and Bacteriology, University of the Philippines)

This report is based on a study of the autopsy records from the department of pathology and bacteriology, of the University of the Philippines, and on statistics of the Philippine Health Service. The total number of records of autopsies examined is 5,400, which were performed over a period of nine years. The report is similar to one from India by Rogers.

AGE INCIDENCE

An examination of Rogers's(5) work on age incidence in India shows his report to be as follows. The great majority of deaths occurs at an early period of life. In his autopsy series although but 2.7 per cent were under 11 years of age, yet 80 per cent of the Hindus and 62 per cent of the Mohammedans were not above 40 years of age, while 52 per cent of the Hindus and 44 per cent of the Mohammedans were not over 30 years of age. Further, only 6 per cent were from 51 to 60 years of age. He also states that these early deaths cannot be fully accounted for by the prevalence of tropical diseases, such as cholera, dysentery, and tropical fevers.

The Philippines, as India, has a high mortality at an early period of life. During 1914, out of a population of 6,925,319 people within the registration area, we find that 55.49 per cent of all deaths occurred between the ages of 0 and 9 years, 72.91 per cent before the age of 40 years, 6.18 per cent between the ages of 40 and 49 years, 5.26 per cent between 50 and 59 years, and 14.96 per cent above 60 years of age. In 0.50 per cent the age is not stated.

The age incidence in Manila, as found by examination of the records of 2,000 consecutive autopsies, shows 36.7 per cent of all deaths to occur before the age of 10 years, 81.05 per cent before the age of 40 years, 8.1 per cent between the ages of 41 and 50 years, and 10.85 per cent above 50 years of age, the average age

[1] Received for publication July, 1917.

at death being 22.98 years, and the average age at death occurring after 11 years being 35.25 years.

When interpreting the high mortality which occurs so early in life, the following must be considered: High infant mortality, tuberculosis, and the tropical diseases, such as cholera, dysenteries, and tropical fevers. During one year the average death rate of Filipino infants less than 1 year of age was 486.77 per 1,000, which is a mortality of almost 50 per cent.

Tuberculosis causes a large number of deaths in all decades. It has been the cause of death in 8 per cent of all infants up to 5 years of age which have come to autopsy in Manila.(4)

The United States Census Bureau calculated in 1912 that 400,000 of the present inhabitants of the Philippine Islands were doomed to die of tuberculosis.

The prevalence of cholera, the dysenteries, tuberculosis, and other diseases in the Philippines are shown in Table I, compiled from the Philippine health statistics.

TABLE I.—*General causes of death and number of deaths in the Philippines during 1914.*

Tuberculosis	18,009
Fevers	22,102
Cholera	2,018
Dysenteries and diarrhœas	12,381
Other infectious diseases	6,048
Beriberi	4,040
Convulsions of infants under 5 years of age	22,057
Leprosy	21
Violence	1,834
Cerebral hemorrhage	581
All other causes	65,938
Total number of deaths	155,029

ATHEROMA

A study of the presence and extent of atheroma with associated cardiac and renal changes in Filipinos was made to determine the possibilities which these changes might have in explaining the cause of death after the age of 40 years.

An examination of Table I shows that only about 58 per cent of all deaths can be accounted for by tuberculosis, infantile convulsions, and the more typical tropical diseases. Thus there are about 42 per cent in which the cause of death has not been specifically recorded. It is safe to say that among this 42 per cent of nonspecifically recorded deaths there is a large percentage of those who live beyond the age of 40 years, as the majority of deaths from the diseases recorded in Table I occurs before the age of 40 years. Also it may be stated that in this 42 per cent

is the majority of those deaths influenced by arterial, cardiac, or renal changes.

TABLE II.—*Percentage of slight and marked atheroma among natives of India in different decades.* (5)

Age in years.	Normal.	Slight.	Marked.	Granular kidney in atheroma cases.
Up to 10	100	0.0	0.0	0.0
11 to 20	93.3	6.7	0.0	0.0
21 to 30	81.3	16.2	2.5	9.8
31 to 40	70.1	24.2	5.7	16.8
41 to 50	52.6	28.0	19.4	16.4
51 to 60	40.6	24.8	34.8	26.8
Over 60	38.1	33.3	28.6	69.2
Up to 40	79.4	13.4	3.2	13.1
Over 40	47.5	27.4	25.1	26.1
Total	72.6	19.4	8.0	18.5

TABLE III.—*Sex and race incidence of atheroma.* (5)

	Males.	Females.	Hindus.	Mohammedans.
Slight atheroma	21.4	13.0	19.5	19.5
Marked atheroma	7.4	9.2	7.3	9.75
Total	28.8	22.2	26.8	29.25
Up to 40 years	22.2	13.8	20.2	21.1
Over 40 years	52.0	57.5	52.5	50.9

Rogers has stated that in India the early deaths cannot be fully accounted for by the prevalence of tropical diseases. This led him to make a study of the arteries, with a view to determining the degree of atheromatous changes which had taken place in the arteries during the different decades. He notes, as the most important point brought out by the analysis, the sudden and great increase of marked arterial degeneration as soon as the age of 40 years is passed. The sex incidence shows only a slight preponderance in males. However, the lesser incidence in Indian females is confined to the slighter degrees of arterial degeneration and to below the age of 41 years, both the more marked degrees of atheroma and the incidence over 40 years of age being actually higher in the females than in the males. The average age of all females in his series is lower than that of the males, 17.7 per cent of the women having been over 40 years of age at the time of death. This is in accordance with the greater frequency of marked atheroma among the females as compared

TABLE IV.—*Percentage of atheroma cases with hypertrophy of heart and chronic interstitial nephritis in different decades of 1,000 Filipinos.*

Ages in decades.	Sexes and total.	Number of cases examined.	Normal arteries.	Slight atheroma.	Marked atheroma.	Hypertrophy of heart in cases of atheroma.	Absence of hypertrophy of heart in cases of atheroma.	Chronic interstitial nephritis in cases of atheroma.	Absence of chronic interstitial nephritis in cases of atheroma.
			Per cent.	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*	*Per cent.*
0 to 10	Males	54	100	0	0	0	0	0	0
	Females	29							
	Total	83							
11 to 20	Males	127	88.19	11.81	0.0	6.66	93.34	6.66	93.34
	Females	50	88.00	10.0	2.0	33.33	66.66	33.33	66.66
	Total	177	88.14	11.3	0.56	14.28	85.72	14.28	85.72
21 to 30	Males	159	81.13	17.07	1.89	6.66	93.34	13.34	86.66
	Females	89	80.89	13.48	5.62	17.55	82.44	11.76	88.24
	Total	248	81.05	15.72	3.22	10.64	89.36	12.76	87.24
31 to 40	Males	123	73.17	15.44	11.38	50.00	50.00	40.00	60.00
	Females	55	61.81	23.63	14.54	33.33	66.66	52.38	47.62
	Total	178	69.66	17.97	12.37	43.14	56.86	45.09	54.91
41 to 50	Males	108	38.88	25.00	36.11	43.93	56.07	59.99	40.01
	Females	36	36.11	22.22	41.66	26.09	73.91	60.87	39.13
	Total	144	38.2	24.3	37.5	39.32	60.68	59.58	40.42
51 to death	Males	121	21.49	13.22	65.29	45.45	54.54	86.32	13.68
	Females	49	12.24	22.44	65.3	37.2	62.8	88.57	11.43
	Total	170	18.82	15.88	65.29	43.55	51.45	86.95	13.05

0 to 40	Males	463	83.8	13.17	3.02	24.00	76.00	22.66	77.34	
	Females	223	80.22	13.45	6.28	27.27	72.73	34.09	65.91	
	Total	686	82.64	13.28	4.08	25.21	74.79	26.88	73.12	
41 to death	Males	229	29.69	18.81	51.52	50.62	49.38	75.15	24.85	
	Females	85	22.35	22.35	55.28	31.81	68.19	78.78	21.22	
	Total	314	27.7	19.76	52.55	44.93	55.07	75.77	24.23	

with the males. He also claims that granular kidney in relation to age incidence certainly increases with each decade parallel to that of atheroma.

The atheromatous change in the arteries of Filipinos was determined by examination of 1,000 bodies in which the arterial changes were definitely recorded. The results obtained are not as conclusive as they might be, but they give a fair estimate of atheromatous changes in Filipinos. Atheromatous and associated cardiac and renal changes are without doubt important factors in the cause of death, at least after 40 years of age.

In tabulating this series of autopsies for atheromatous changes, I have included sex, ages in decades, hypertrophied and normal hearts, and chronic interstitial nephritis and normal kidneys, noting whether or not they were associated with atheroma. Atheroma was divided into slight and marked changes; it was called slight when there were a few patches here and there throughout the aorta or in the coronaries, while those cases were called marked which showed numerous large patches, calcification, or ulcerative changes. A kidney was called chronic interstitial nephritis if it showed fibrosis, multiple small cysts, chronic diffuse nephritic changes, or arteriosclerotic changes. The heart was called hypertrophied from increase in size and weight, and it was not specified as to whether or not it was the entire heart.

The results obtained from an examination of the arteries, hearts, and kidneys of 1,000 Filipinos are summarized in Table IV.

DISCUSSION OF ATHEROMA

The successive decades between 0 and 40 years show a more or less constant and proportional increase of atheroma with associated hypertrophy of the heart and chronic interstitial nephritis. However, the decades between 41 years of age and death show a sudden great increase of atheroma with associated hypertrophy of the heart and chronic interstitial nephritis. This great increase of all three associated conditions is the most significant and important fact brought out by the tables and at least is indicative that they are probably a large factor in the cause of death after 41 years of age. The tabulation of the changes as they occurred in each sex does not show any great difference between the sexes. Of those examined for atheroma who lived beyond the age of 40 years, 23.84 per cent were females. However, a greater percentage of the females over 40 years of age showed atheromatous changes than did the males, while under the age of 40 years a smaller percentage of females showed

atheromatous changes than did the males. The heart changes recorded show that after the age of 40 hypertrophy of the heart as associated with atheroma is found to occur in the males almost twice as frequently as in the females. The kidney changes recorded show that after the age of 40 years chronic interstitial nephritis is found almost as frequently in the females as in the males and is found in both on an average of 75.77 per cent.

ETIOLOGIC AGENTS OF ATHEROMA

Among the conditions which enter for consideration as possible factors in producing atheroma with its associated heart and kidney changes in Filipinos are increased blood pressure, syphilis, strains, alcohol, and chronic intestinal disorders.

Blood pressure.—Recently the blood-pressure picture in Filipinos was determined by Concepcion and Bulatao.(2) Their experiments show that the average blood pressures in Filipinos expressed in millimeters of mercury are as follows: Between the ages of 15 and 40 years the systolic pressure is 114.45, the diastolic pressure 80.76, and the pulse pressure 33.69; above the age of 40 years the systolic pressure is 131.27, the diastolic pressure 88.72, and the pulse pressure 42.55. The systolic pressure of the Filipinos is very much lower than that of Americans living in temperate climates (Woley), but is the same as that of Americans living in the tropics whose ages range between 18 and 50 years, the average being 26.6 years.(1) These findings suggest that in the tropics systolic pressures are very much lower than in temperate climates and that with increase of age there is a general rise of systolic, diastolic, and pulse pressures in the Filipinos.(2)

An examination of the preceding statements, which give a fair estimate of the blood-pressure picture in Filipinos, is at least indicative that blood pressure is not a primary factor in producing atheroma in Filipinos.

Syphilis.—Syphilis appears to be on the increase in the Philippines, but will only be mentioned from a statistical view. The amount of syphilis cannot be stated in percentage for the entire Islands, but the Wassermann laboratories show it to be very common. A conservative estimate regarding the number of patients treated in the Philippine General Hospital suffering from syphilis was 3 per cent. Although the Philippine Health Service reported that 1.4 per cent of 16,431 cases were treated in the wards of the Philippine General Hospital during 1914 for syphilis, this did not include the incidence in 25,000 or more dispensary cases, which would undoubtedly make a much higher

percentage. Also it does not include other conditions which in some instances are no doubt of syphilitic origin, such as still-births. A review of 712 autopsies at Manila,(3) performed during 1913, showed 21 cases presenting recognizable syphilitic lesions. However, there were only 11 of these occurring in Filipinos, but of these 11 there were 9 cases where the aorta was involved. This substantiates a fact mentioned by Crowell that where syphilis is recognized at autopsy in Filipinos the vascular lesions are the most frequent. In my series of 1,000 atheroma cases 4.33 per cent were definitely recognized as syphilitic in origin. There is the probability that a number of syphilitic atheroma cases were masked by an extensive atheroma other than syphilitic and were thus overlooked at autopsy.

Chronic intestinal disorders.—A personal examination of the entire intestinal contents of more than 1,000 autopsies shows that the intestines of from 80 to 90 per cent of subjects are laden with fæcal material containing one, two, or more types of intestinal zoöparasites. It seems evident that such a condition extending throughout years must produce a chronic toxæmia of intestinal origin. Clinical observation shows that constipation is the rule rather than the exception among the class of patients entering the hospitals. From the amount of data at hand on this subject any conclusion is hypothetical, but basing such a conclusion on the preceding statements, it appears that chronic intestinal disorders leading to chronic toxæmia are probably an important factor in the production of atheroma in Filipinos.

Strains.—Strains resulting from heavy and continued manual labor are found among such classes as farmers and stevedores, and a small percentage is found among workers in mines and railroads. However, the Philippines does not possess the industries which require large numbers of laborers who perform heavy manual labor over a long period of time. The women of the working classes usually perform heavy work, such as carrying burdens on their heads. On the whole, it is doubtful whether any importance can be placed on strains as a prime factor in producing atheroma or other arterial changes among the people of this country.

Alcohol.—Alcoholic drinks are partaken of by the Filipinos throughout the Islands, but not as a rule to the extent of intoxication. It is rare that a Filipino is seen under the influence of alcohol. There are a number of locally made drinks, such as tuba, tapuy, vino, basi, and ginebra, some of which contain large

amounts of alcohol. Statistics compiled by the Bureau of Internal Revenue show that there is an annual domestic consumption of between nine and ten million proof liters of locally distilled spirits. This does not include the spirits from illicit stills. The statistics for 1915 showed that there were found in the Islands 103 illicit stills, while there were 75 registered stills. The above statistics do not include imported spirits.

ANEURISMS

The aneurism incidence as seen at autopsy in Filipinos has been tabulated primarily for comparison with Rogers's determination of aneurism incidence in the natives of India. A knowledge of the incidence of aneurisms in tropical people may also be of value for comparison with their incidence in people of temperate climates. Such a comparison may throw light upon the alleged greater virulence of oriental syphilis, in so far as this may be manifested by the production of aneurisms. Practically all of the aneurisms of this series have been found in cases of sudden death, and all showed evidences of syphilis other than the aneurism itself.

Rogers reports that the post-mortem records of the Calcutta Medical College showed 30 aneurisms among 5,900 autopsies, making an incidence of 0.5 per cent, although among the natives alone the aneurism incidence was 0.36 per cent. He claims that syphilis is appallingly common among the class of natives who enter the hospitals.

TABLE V.—*Race incidence of aneurisms in India.* (5)

Race.	Aneurisms.	Proportion.	Subjects.	Race incidence.
Europeans	9	31.1	7.0	2.2
Hindus	11	37.9	67.4	0.28
Mohammedans	8	27.6	21.8	0.62
Native Christians	1	3.4	3.8	0.45
Total	20	68.9	93.0	0.36

In determining the incidence of aneurisms in Filipinos, I have included all aneurisms found in 5,400 autopsies. The race, sex, and age incidence are summarized in Table VI, while Table VII shows the more important features of an analysis of all the aneurisms with the associated lesions of rupture, atheroma, chronic interstitial nephritis, and hypertrophy of the heart.

TABLE VI.—*Race, sex, and age incidence of aneurisms in the Philippines as seen at autopsy.*

Race.	Autopsies examined.	Aneurisms.	Average age of occurrence.	Race incidence.	Sex incidence.	
					Males.	Females.
			Years.	*Per cent.*	*Per cent.*	*Per cent.*
Filipinos	4,969	19	43.42	0.382	89.5	11.5
Chinese	228	10	42.12	4.34	100.0	0.0
Japanese	54	1	26.0	1.85	0.0	100.0
Americans	114	9	39.2	7.88	100.0	0.0
Europeans	35	1	42.0	2.08	100.0	0.0
Total	5,400	40				

Table VI, it will be seen, shows the aneurism incidence in Filipinos to be 0.382 per cent, which is very low when compared with the aneurism incidence in Chinese, 4.34 per cent, and the aneurism incidence in Americans, 7.88 per cent. This low aneurism incidence in Filipinos is similar to the low aneurism incidence in the natives of India, which Rogers gives as 0.36 per cent.

ETIOLOGIC AGENTS AND LESIONS ASSOCIATED WITH ANEURISMS

Syphilis.—Syphilis is probably the cause of all the aneurisms of this series, and in all cases there were other associated lesions of syphilis, such as arteritis, gummata, and osteitis. The prevalence of syphilis in the Philippines is discussed under atheroma.

Blood pressure and strains.—In this series of aneurisms there could not be obtained any reliable histories or recorded blood pressures. Some of the cases in Filipinos occurred in farmers and sailors, while in the Chinese some occurred in those who performed heavy manual labor; in the Americans and Europeans the cases varied from those who performed heavy manual labor to those who did clerical work. The case occurring in a Japanese was in a prostitute.

Hypertrophy of the heart.—Hypertrophy of the heart occurred in 67.5 per cent of all cases, while 32.5 per cent were either normal in size or smaller than normal.

Chronic interstitial nephritis.—Chronic interstitial nephritis occurred in 65 per cent of all the cases, while 35 per cent showed apparently normal kidneys.

TABLE VII.—*Classification of aneurisms and associated lesions as seen at autopsy.*

Artery affected.	Aneurisms.	Per cent.	Atheroma.		Hypertrophy of heart.		Chronic interstitial nephritis.		Site of rupture.								
									Pericardial sac.	Pleural sacs.		Abdomen.	Bronchi.	Œsophagus.	Mediastinum.	Trachea.	Not ruptured.
			Slight.	Marked.	Present.	Absent.	Present.	Absent.		Right.	Left.						
Ascending arch of aorta	17	42.5	3	14	12	5	9	8	9	0	0	0	0	0	0	0	8
Transverse arch of aorta	8	20.0	0	8	4	4	5	3	1	0	2	0	1	0	1	2	1
Descending thoracic aorta	11	27.5	0	11	8	3	8	3	0	0	4	0	1	2	0	0	4
Abdominal aorta	1	2.5	1	0	1	0	1	0	0	0	0	1	0	0	0	0	0
Subclavian artery	1	2.5	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0
Femoral artery	1	2.5	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1
Cerebral artery	1	2.5	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1
Total	40	100.0	4	36	27	13	25	15	10	1	6	1	2	2	1	2	15

Atheroma.—Atheroma occurred as marked atheroma in 90.0 per cent of all cases and as slight atheroma in 10.0 per cent. The type of atheroma in all cases was syphilitic, although in several cases there was associated the calcified type seen in old age. However, from a preceding statement under atheroma that 4.33 per cent of all our atheroma cases were syphilitic, and since the majority of gross syphilitic changes in Filipinos are seen in the arteries, while the aneurism incidence is only 0.382 per cent, there is evidently a large excess of syphilitic arteritis to form a base for aneurism formation. It would be safe to conclude that syphilis of the vessels does play an important part in the production of aneurisms in Filipinos.

DISCUSSION

Here in the Philippines an examination of the autopsy records shows a low aneurism incidence among Filipinos, 0.382 per cent, which is similar to the low aneurism incidence seen at autopsy among the natives of India (0.36 per cent). From this low incidence of aneurisms in the races, it seems that syphilis in the tropics has less predilection for the arteries of the natives than it has for the arteries of northern races residing in the tropics. Probably what is more nearly correct is that syphilis produces more pathologic effects on the arteries of northern races in the tropics than it does upon the native born.

The high aneurism incidence as found among the Americans is considerably in error, because the majority of the American dead examined at the city morgue are examined on account of unexplained sudden death, while the larger number of dead Americans are not autopsied. Nevertheless, in consideration of the fact that there are only about 0.15 per cent as many Americans residing in the Islands as Filipinos, it appears that the aneurism incidence in Americans in Manila is considerably greater than in Filipinos.

There were five cases in which there occurred multiple aneurisms. In one case two aneurisms were found, one affecting the femoral artery and the other the ascending aorta, which is reported more completely as follows:

A CASE OF ANEURISM OF THE FEMORAL ARTERY AND OF THE AORTA

A survey of the aneurisms found in the 42,000 clinical records from the Philippine General Hospital and the 5,400 autopsy records from the College of Medicine and Surgery, of the University of the Philippines, shows that this case is the only femoral aneurism recorded. However, primarily the case is reported on account of the large size of the femoral aneurism.

History.—The patient is a Chinese male whose age is 41 years. He entered Bilibid Prison on January 18, 1916, for a term of four months' detention and was admitted to the prison hospital complaining of a continual chest pain which had been present for the past two months. The pain was first noticed after performing heavy manual labor, and it has become so severe that the patient breathes with difficulty. (No further description of the pain is recorded.) Upon further physical examination a large pulsating tumor was found in the right inguinal region below Poupart's ligament. The patient had not complained of this pulsating tumor, but had applied some form of dressing, which produced necrosis of the tissues over the apex, and this was accompanied by continual oozing of blood. The entire right lower extremity is œdematous, and the skin is tightly stretched. No definite history could be obtained concerning the length of time that the tumor mass was present nor concerning syphilitic infection.

Laboratory report.—A Wassermann test performed by the Bureau of Science, January 24, 1916 (37931-C), was negative.

The urine was normal.

A tentative diagnosis was made of malignant tumor or aneurism. The surgeon in charge advised an operation to prevent the loss of blood from the tumor mass.

Operation.—Spinal anæsthesia was employed by using 80 milligrams of stovaine. The stovaine was administered at 3.35 in the afternoon, January 24, 1916, and the operation began at 4.15 and was completed at 4.41.

An incision was made over Poupart's ligament, and the iliac artery was ligated extraperitoneally above the tumor mass. A section of tissue from the apex was removed for histological examination; it showed evidences of an arterial wall. The entire right lower extremity was then placed in hot packs. The patient appeared to be in very good condition when seen at 8.30 in the evening, but suddenly died at 9.15, January 24, 1916, about four and one-half hours after the operation.

The autopsy findings are as follows. Anatomical diagnosis: Chronic aortitis with aneurismal dilatation of the aorta (syphilitic); chronic parenchymatous degeneration of the heart (syphilitic); aneurism of the femoral artery (syphilitic); chronic diffuse nephritis; pneumonoconiosis; chronic miliary tuberculosis of the lungs; chronic adhesive fibrous pleuritis; and some œdema and congestion of meninges.

The body is that of a rather large, poorly nourished, adult Chinese male, aged 41. The skin is yellowish brown. The hair is black, straight, coarse, rather long, and limited to the pubes, axillæ, and scalp. The eyes are apparently normal. The teeth are carious, and the mucosa of the mouth is pale and somewhat necrotic over the gums. Rigor mortis is present throughout the body, and suggillation is present on the dependent portions of the body. Lying in the right femoral region involving an area over Scarpa's triangle there is a firm, bulging, hemispherically shaped mass which measures from 10 to 12 centimeters in diameter; its apex is 5 to 6 centimeters above the surrounding skin surface. The skin covering the mass is tightly stretched, but apparently normal, except at the apex, where it has a greenish necrotic appearance, and upon pressure some thin blood-tinged fluid oozes from it. After dissecting the skin from the entire mass and opening it, it is found to be filled with newly formed blood clot, which has the consistence of chicken fat. The walls of the mass are formed by a dilatation of the femoral artery producing an elongated, irregular, ovoid-

shaped aneurism which measures 11 to 12 centimeters in the long diameter and 7 to 8 centimeters in the short diameter. The walls are firm and retain their shape. They measure 3 to 4 millimeters in thickness. The intimal surface of the aneurism is roughened in numerous places with flat, soft yellowish plaques which average 0.5 to 1 centimeter in diameter and about 2 millimeters in thickness.

The upper extremity of the aneurism lies immediately below Poupart's ligament, while the lower extremity lies at the opening of Hunter's canal. Both the iliac artery leading into the aneurism and the continuation of the femoral artery from the aneurism are apparently normal.

An operative wound had been made over Poupart's ligament, and the iliac artery had been ligated just above the aneurism.

On section of the body there is found a very small amount of subcutaneous fatty tissue. The muscle is a pale reddish brown and is somewhat soft in consistence.

Abdomen.—The serosa of the small intestine has a light grayish color, that of the large intestine is rather pale, and the entire serosa is moist. The abdominal cavity itself is moist, but does not contain any free fluid. The diaphragm is located at the fifth rib on the right and the sixth on the left side. The abdominal viscera lie in normal relationship to each other.

Thorax.—The thymus is atrophied.

Pleural sacs.—Both pleural sacs are obliterated with fibrous adhesions over the apex and somewhat posteriorly, while anteriorly they are free from adhesions. The parietal pleura has a grayish color, while the visceral pleura shows a blackish color over most of its surface.

Lungs.—The lungs themselves are very large. The entire upper lobes of both lungs are consolidated and hard in consistence. On section the upper lobes cut with very much resistance, showing a surface which is smooth, very compact, and black, but in some places there are elevated whitish areas of 1 to 2 millimeters in diameter, the entire cut surface having the appearance as though cutting through a lump of coal. The lower lobes of both lungs are voluminous and float high in water, although the upper portion of the lower lobe of the right lung shows a condition similar to the upper lobes of both lungs. Section through the lower lobes shows a rather smooth surface of normal compactness which is greenish black and moist. The bronchi have a reddish color and contain mucoid material.

Heart.—The parietal pericardium is pale, smooth, and thin. The pericardial sac is about normal in size and shape and is free from adhesions; it contains a normal amount of fluid. The epicardium is rather pale and covers some fat; in the other places it is smooth and thin. The heart itself is somewhat enlarged, the tricuspid valve admitting almost four fingers, the mitral valve barely three. The left auricle is considerably distended with blood, and the right auricle is also distended with blood, while the right ventricle and left ventricle both appear to be enlarged, and the walls are slightly thicker than normal. The muscle is pale brown and is very soft and rather flabby; the cut surface is smooth and dull. The endocardium covering the aortic and mitral valves is somewhat thickened, while throughout the remaining portion of the heart it is pale, smooth, and thin. The blood is coagulated, forming coagulum of chicken-fat consistence.

Aorta.—The aorta extending from the aortic valve up to and involving the transverse arch is considerably dilated and at one place shows an outpouching over a circular area of 6 to 7 centimeters. This outpouching is as

much as 2 centimeters deep in places and begins just above the aortic valve. The walls of the entire portion are inelastic, and the intima is roughened with plaques which are flat, soft, elevated, and whitish to yellowish. These plaques measure from 0.5 to 1 centimeter in diameter and about 2 millimeters in height. Throughout the remaining portion of the thoracic and abdominal aorta the intima shows the presence of some whitish to yellowish elevated plaques of 0.5 to 1 centimeter in diameter. The iliac arteries are apparently normal.

Spleen.—The spleen is about normal in size and rather soft and is bluish gray. The capsule is smooth. The spleen cuts with some resistance, showing a smooth reddish surface upon which the interstitial tissue is prominent. From the cut surface exudes some blood-tinged fluid.

Adrenals.—The adrenals show no appreciable change from normal.

Kidneys.—The kidneys are about one and a half times the normal in size, but they are about normal in shape. They are surrounded by a small pad of fat, and they are firm. They cut with resistance, showing a smooth surface upon which the pyramids are regular in outline and pale, with a pinkish tint and with some red linear markings at the bases; while the cortex varies in thickness, from thinner to thicker than normal, and the entire cortex is pale, with a pinkish tinge, and appears to be minutely granular. The capsule strips with considerable resistance, showing a surface which is smooth in places and somewhat roughened in others and which is pale. The pelves are apparently normal.

Intestines.—The intestines are apparently normal.

Liver.—The liver is brownish. The capsule is smooth. It is about normal in shape and size. It cuts easily; upon the cut surface the lobules are plainly visible, although they appear to be slightly paler than normal, and the outlines are pale. The bile ducts and vessels show no appreciable change. The gall bladder contains some thick, viscid greenish bile, and its mucosa and walls are apparently normal.

Urinary bladder.—The urinary bladder is contracted and empty. Its mucosa is pale and smooth throughout.

Brain.—The dura mater strips easily and is pale and smooth. Beneath the pia-arachnoid there is an excess of watery fluid, but the vessels show no appreciable change from normal.

HISTOLOGY

Sections were made from the femoral aneurism and from the aneurismal dilatation of the aorta. The sections included a raised plaque upon the intima and were stained with hæmatoxylin and eosin and were also stained for spirochætes by the Levaditi method.

Aneurism walls.—There is a thickening of the intima which is composed of a noncellular hyalinlike substance which has its continuity broken in places. The media in places is infiltrated with round cells, which produce a slight spreading of the muscle fibers. The blood vessels of the tunica externa have thickened walls and narrowed lumens and are surrounded with dense, round-cell infiltration and some endothelial leukocytes.

Aortic walls.—The aortic walls resemble the aneurism walls with the exception that there is more extensive cellular infiltration of the media with degeneration and a new-forming compact tissue. The vasa vasorum are also more extensively involved than are those of the femoral vessel.

The sections stained by the Levaditi method do not reveal any structures

which can be absolutely identified as *Treponema pallidum*, but there are structures which resemble them.

Heart muscle.—Sections of the heart muscle stained by the Levaditi method do not reveal any evidence of *Treponema pallidum*.

CONCLUSIONS

1. The average duration of the life of Filipinos is shown by the statistics of the Philippine Health Service to be considerably below 40 years.

2. The cause of death before 40 years of age in the greater percentage of Filipinos is due to the tropical diseases.

3. The incidence of atheroma with associated hypertrophy of the heart and chronic interstitial nephritis increases suddenly after 40 years of age; this is an important factor in the cause of death after 40 years of age.

4. Chronic intestinal disorder leading to chronic toxæmia is probably the most important factor in producing such a high percentage of atheroma.

5. The aneurism incidence of Filipinos as seen at autopsy is 0.382 per cent.

6. The chief manifestation of syphilis in Filipinos, as seen at autopsy, is in the arteries in 80 to 90 per cent of the cases.

7. High blood pressures and strains do not appear to be important factors in the production of atheroma in Filipinos and probably not in the production of aneurisms.

8. These findings concerning vascular lesions seen at autopsy in the Philippines agree closely with the findings of Rogers in India.

REFERENCES

1. Chamberlain, W. P. A study of the systolic blood pressure and the pulse rate of healthy adult males in the Philippines, *Phil. Journ. Sci., Sec. B* (1911), 6, 467.

2. Concepcion, I., and Bulatao, E. Blood pressure picture of the Filipinos, *ibid.* (1916), 11, 135, 151.

3. Hammack, R. W. Syphilis in 712 autopsies. Reported before the Manila Medical Society (1914).

4. Mendoza-Guazon, Maria Paz. Study of the anatomicopathologic lesions in one thousand Filipino children under five years, *Phil. Journ. Sci., Sec. B* (1917), 12, 51.

5. Rogers, L. Gleaning from the Calcutta post-mortem records, *Ind. Med. Gaz.* (1910), 45, 84–90, 124–127.

6. Woley, H. P. The normal variation of the systolic blood pressure, *Journ. Am. Med. Assoc.* (1910), 55, 121.

SUBSTITUTION OF HUMAN BLOOD CELLS BY MONKEY'S RED CORPUSCLES IN PERFORMING THE COMPLEMENT FIXATION TEST FOR SYPHILIS [1]

By Otto Schöbl and Carlos Monserrat

(From the Serum Section of the Biological Laboratory, Bureau of Science, Manila)

The absence of natural hæmolytic amboceptor in human serum makes the use of antihuman amboceptor and human red cells preferable to those methods which employ antisheep hæmolytic system. However, there is a practical difficulty connected with this method, namely, the comparatively low titer of the antihuman amboceptor as usually obtained by immunization of rabbits with human red corpuscles. A considerable number of injections is necessary, and strictly fresh blood not always being available to a laboratory worker who happens to be without direct connection with a hospital or a similar institution, a high percentage of rabbits die before they yield serum strong enough to be useful for a test.

It occurred to us that, on account of the biologic relationship, monkey's red cells may probably behave in a similar way as human corpuscles in this respect. These animals, common in tropical countries, are inexpensive and easily maintained about the laboratory. Thus a supply of fresh blood is always at hand, since repeated bleedings taken directly from the animal's heart are tolerated without any apparent harm to the animals.

In order to establish the usefulness of monkey's red cells in performing the complement-fixation test for syphilis, the following question had to be answered:

1. It had to be determined whether or not human serum contains natural hæmolytic amboceptor toward monkey's red corpuscles.

2. The practicability of producing high value antimonkey hæmolytic amboceptor had to be established.

3. A series of comparative tests with sera submitted for routine examination had to be carried out to determine if there is any lessening in the accuracy of the test when monkey's red corpuscles are used as compared with the method in which human red cells are employed.

[1] Received for publication June, 1917.

With these points in view the following experiments were undertaken, the arrangement of which is evident from the tables.

TABLE I.—*Showing the results of searching for natural hæmolytic amboceptor toward monkey's red cells in human sera.*

[c. h., complete hæmolysis; m. h., moderate hæmolysis; s. h., slight hæmolysis; v. s. h., very slight hæmolysis; n. h., no hæmolysis.]

0.2 c. c. of inactivated patient's serum. Specimen No.—	Result after 0.5 c. c. of 4 per cent suspension of monkey red cells and complement 1:10.	Result after 0.5 c. c. of 4 per cent suspension of sheep cells and complement 1:10.	0.2 c. c. of inactivated patient's serum. Specimen No.—	Result after 0.5 c. c. of 4 per cent suspension of monkey red cells and complement 1:10.	Result after 0.5 c. c. of 4 per cent suspension of sheep cells and complement 1:10.
11260	n. h.	c. h.	C O	n. h.	c. h.
11079	n. h.	m. h.	M M	n. h.	c. h.
11553	n. h.	v. s. h.	V B	n. h.	c. h.
14627	n. h.	v. s. h.	V N	n. h.	c. h.
9276	n. h.	c. h.	V R	n. h.	c. h.
5998	n. h.	c. h.	C G	n. h.	c. h.
32876	n. h.	n. h.	P	n. h.	c. h.
41258	n. h.	n. h.	A V	n. h.	m. h.
89477	n. h.	n. h.	R M	n. h.	c. h.
11532	n. h.	m. h.	F H	n. h.	c. h.
A A	n. h.	n. h.	G Y	n. h.	s. h.
T V	n. h.	s. h.	V G	n. h.	c. h.
P L	n. h.	c. h.	49530	n. h.	c. h.
H L	n. h.	n. h.	42008	n. h.	c. h.
M O	n. h.	c. h.	42276	n. h.	m. h.
N A	n. h.	c. h.	42289	n. h.	c. h.
G M	n. h.	c. h.	P G	n. h.	s. h.
Y B	n. h.	n. h.	M K	n. h.	c. h.
F C	n. h.	v. s. h.	M E	n. h.	c. h.
F A	n. h.	n. h.	M W	n. h.	c. h.

It is evident from the results of the tests of 40 sera collected at random over a period of several months that none of them, in the quantity used, contained a sufficient amount of natural amboceptor to cause hæmolysis when brought in contact with red corpuscles of monkey and guinea pig's complement. However, the majority of the same sera contained a considerable amount of antisheep natural hæmolytic amboceptor.

ANTIMONKEY HÆMOLYTIC AMBOCEPTOR

The difficulty in production of high-value antihuman hæmolytic amboceptor has been already mentioned in this paper. In our experience the average number of injections necessary to produce useful serum amounted to at least five injections and the resulting

serum averaged 100 units per cubic centimeter, rarely 150, and never more than 200 units per cubic centimeter. Simultaneous intravenous and intraperitoneal injections gave the best results. Allowing an interval of four days between injections, from 10 to 15 cubic centimeters of serum were obtained in twenty-six days. That is to say, one rabbit yielded from 1,000 to 1,500 units. However, sera of not more than 50 units per cubic centimeter were frequently obtained. Considering the high mortality of the treated animals and the poor condition of the survivals, it will be appreciated that the production of antihuman hæmolytic amboceptor requires a great many animals and involves a good deal of work, time, and expense.

Following are the records of animals immunized with monkey's red corpuscles.

Rabbit 1 received the usual number of injections of washed monkey's red cells, that is, five injections intravenously and five injections intraperitoneally at the same time. The period of immunization extended over fifteen days. Five days after the last injection the animal was bled. Two days later another bleeding was taken from the heart. Altogether 25 cubic centimeters of serum were obtained by both bleedings. The mixture of the two sera tested 4,000 units per cubic centimeter. The total amount of monkey's blood used for immunization was 7.30 cubic centimeters. This rabbit, three weeks after the immunization began, yielded 100,000 units and survived, thus being available for other purposes.

Rabbit 2 received three injections within eight days. The total amount of blood injected was 4.50 cubic centimeters. Five days after the last injection the serum of this animal tested 2,000 units per cubic centimeter.

Rabbit 3 received only two injections of monkey's red cells. The total amount of blood was 2.50 cubic centimeters. Its serum tested 100 units per cubic centimeter.

Rabbit 4 received but one injection of monkey's red cells. When tested five days after the injection, the serum had a titer of less than 20 units per cubic centimeter.

Following the usual scheme of immunization, in rabbit 1 a serum was obtained in three weeks, which was twenty times higher than the best average antihuman hæmolytic serum; in rabbit 2 ten times higher serum was obtained in two weeks; and rabbit 3 yielded in nine days serum of the same titer as the average antihuman amboceptor obtained after five injections.

Rabbit 4, after one injection, gave serum of 20 units per cubic centimeter.

It follows from these experiments that two injections of monkey's red cells are sufficient to produce serum of 100 hæmolytic units per cubic centimeter, which is useful serum for tests. This can be accomplished within thirteen days, using not more than from 2.5 cubic centimeters to 3 cubic centimeters of blood.

In Table II the results of comparative tests are given. In one series antihuman amboceptor and human red cells were used; in the other the same specimens of blood were subjected to a test in which antimonkey hæmolytic system was employed. Otherwise the arrangement of the tests was identical in both series.

TABLE II.—*Showing comparative tests with antihuman and antimonkey hæmolytic system.*

Specimen.	Antihuman hæmolytic system.		Antimonkey hæmolytic system.	
	Alcoholic antigen.	Cholester antigen.	Alcoholic antigen.	Cholester antigen.
M T	pos. ±	pos. +	pos. ±	pos. +
11967	neg.	pos. +	neg.	pos. +
10194	pos. 6 +	pos. 6 +	pos. 6 +	pos. 6 +
41770	neg.	pos. +	neg.	pos. +
C H	neg.	neg.	neg.	neg.
M	pos. ±	pos. ±	pos. ±	pos. ±
W	pos. 6 +	pos. 6 +	pos. 6 +	pos. 6 +
G	pos. ±	pos. ±	pos. ±	pos. ±
D	neg.	neg.	neg.	neg.
41824 C	pos. 3 +	pos. 3 +	pos. 3 +	pos. 3 +
FW	neg.	neg.	neg.	neg.
42195	pos. +	pos. 3 +	pos. +	pos. 3 +
42009	neg.	pos. 3 +	neg.	pos. 3 +
C C	neg.	pos. 3 +	neg.	pos. 3 +
M T	pos. +	pos. 6 +	pos. +	pos. 6 +
Or	neg.	neg.	neg.	neg.
42008	pos. ±	pos. +	pos. ±	pos. +
42276	pos. +	pos. 5 +	pos. +	pos. 5 +
42289	pos. 3 +	pos. 6 +	pos. 3 +	pos. 6 +
M G	neg.	pos. ±	neg.	pos. ±
M H	neg.	pos. ±	neg.	pos. ±
Mc C	neg.	neg.	neg.	neg.
Y K Y	neg.	neg.	neg.	neg.
12094	pos. 2 +	pos. 3 +	pos. 2 +	pos. 3 +
42312	pos. 3 +	pos. 6 +	pos. 3 +	pos. 6 +
M D	neg.	neg.	neg.	neg.
41841	pos. 5 +	pos. 6 +	pos. 5 +	pos. 6 +

Table II shows that the results of the complement fixation test with antimonkey amboceptor and monkey's red cells were identical with those obtained when antihuman hæmolytic system was employed.

CONCLUSIONS

1. Human sera in quantities used for test were found to contain no antimonkey natural hæmolytic amboceptor.

2. Hæmolytic sera of higher value can be obtained by immunization of rabbits with monkey's cells than it is possible by immunization with human red corpuscles.

3. Comparative tests for diagnosis of syphilis carried out on samples collected at random gave identical results, whether antihuman or antimonkey hæmolytic system was used.

Issued with THE PHILIPPINE JOURNAL OF SCIENCE, SECTION B,
Tropical Medicine, Vol. XII, No. 5, September, 1917.

PROCEEDINGS OF THE MANILA MEDICAL SOCIETY

REGULAR MONTHLY MEETING, APRIL 2, 1917

The regular monthly meeting of the Manila Medical Society was held at 8.30 in the evening, April 2, 1917, in the College of Medicine and Surgery, with President Winter in the chair and with 12 members and 2 guests present.

Upon the suggestion of the president it was moved and seconded that the reading of the minutes of the last meeting be dispensed with, and the following applications for active membership in the society were recommended by the council for ratification by the society:

Lieut. Col. Joseph Taylor Clarke, M. C., U. S. Army.	Dr. Lane Bruce Kline. Dr. José Eduque.
Capt. Hew Bernard McMurdo, M. C., U. S. Army.	Dr. José S. Hilario.

Colonel Manly moved that the society ratify the recommendation. The motion was seconded by Doctor Crowell, and the society voted favorably.

The society then voted to suspend its regular monthly meeting during May, June, and July and again to resume the meetings in August.

A vote of thanks was extended to the outgoing committee, who had so excellently arranged the program for the past three months. The program committee for August, September, and October was announced as appointed by the president:

Dr. C. H. Manlove. Dr. Daniel de la Paz. Capt. J. M. Willis.

Professor E. D. Merrill was not present to read his paper on Contact Poisons.

H. G. MAUL,
Secretary-Treasurer,
Manila Medical Society.

SCIENTIFIC PROGRAM

TREATMENT OF INTESTINAL AMŒBIASIS WITH SPECIAL REFERENCE TO IPECAC AND ITS DERIVATIVES[1]

By DR. B. C. CROWELL

Questions which have assumed importance in intestinal amœbiasis, aside from the pathogenicity of species, are the problem of

[1] This paper has been published in the *Journ. Am. Med. Assoc.* (1917), 69, 6.

carriers, the importance of species pathogenicity in treatment, and the periodicity of appearance of entamœbas. These are discussed. The experimental treatment of amœbic dysentery with ipecac and its derivatives is reviewed, and particular attention is given to Dobell's successful results with the emetine-bismuth-iodide preparation of Du Mez in amœbic dysentery cases and in amœba cyst carriers.

DOES THE IRRITANT ACTION OF EMETINE HYDROCHLORIDE EXTEND TO THE KIDNEY?

By Drs. DANIEL DE LA PAZ AND R. MONTENEGRO

The work was carried out in order to ascertain the irritant effect of hypodermic injection of emetine hydrochloride on the kidney. One milligram per kilogram of dog's weight was injected daily. Six dogs were used as controls: two received hypodermic injection of uranium nitrate, and four received a daily injection of sterile saline solution. The emetinized dogs died with typical symptoms of emetine poisoning. Emetine caused, in two dogs out of four, ecchymoses at the sites of injection, but in no case did its irritant action extend to the kidneys, although the drug eventually killed the animals.

R. B. GIBSON,
Editor of the Proceedings,
Manila Medical Society.

Issued with THE PHILIPPINE JOURNAL OF SCIENCE, SECTION B,
Tropical Medicine, Vol. XII, No. 5, September, 1917.

PROCEEDINGS OF THE MANILA MEDICAL SOCIETY

REGULAR MONTHLY MEETING, AUGUST 6, 1917

The regular monthly meeting of the society was held at 8.30 in the evening, August 6, 1917, at the College of Medicine and Surgery, with President Ruth presiding. There were 33 members present and 8 visitors. The business brought before the society follows.

The minutes of the last meeting were read and approved as read.

The application of Major C. C. Billingslea, M. C., U. S. Army, for active membership was recommended by the council to the society for ratification. The secretary was instructed to place the name of Major Billingslea on the list of active members and then to transfer it to the nonresident list. It was also approved that Major Billingslea be informed by letter of the action taken and that upon his return to Manila he will be again taken up as an active member.

Doctor Crowell moved that the society accept the resignation of Colonel Francis A. Winter and that a letter be drafted and sent to him expressing the regret of the members in his departure and appreciation of his efforts as president of the society. The motion was seconded, and the society voted favorably.

H. G. MAUL,
Secretary-Treasurer,
Manila Medical Society.

SCIENTIFIC PROGRAM

FURTHER OBSERVATIONS ON THE TREATMENT OF YAWS WITH CASTELLANI'S FORMULA

By DRS. LUIS GUERRERO, E. DOMINGO, and M. ARGÜELLES[1]

The high price and shortage of salvarsan and neosalvarsan (undoubted specific remedies for yaws) and objection on the part of patients to injection have made desirable the use of Castellani's formula for this disease. This formula consists of tartar emetic 0.065 gram, sodium salicylate 0.650 gram, potassium iodide 4.000 grams, sodium bicarbonate 1.000 gram, and water to make 30

[1] Presented by Doctor Domingo.

cubic centimeters. Children are given proportionate doses. On the first day one third of the dose is given three times in 120 cubic centimeters of water; on the second day, one dose twice; and on succeeding days, one dose three times daily. Administration of the formula is continued over from ten to fifteen days, and after an interval of from five to ten days is repeated for from five to fifteen days more. Of the 43 Filipino cases in which the treatment was continued, 24 completely recovered, 7 showed improvement of symptoms, 5 had relapses in two to five months after the lesions had entirely healed, and 7 showed no improvement. The results confirm Castellani's observation that the diverse manifestations of yaws heal under the influence of this formula. The treatment is particularly effective in recent infections. We believe that the continuation of the treatment after the lesions have healed (from five to ten days' treatment with intervals of from ten to fifteen days) will insure a permanent cure.

BONE AND JOINT LESIONS OF YAWS WITH X-RAY FINDINGS IN TWENTY CASES

By CAPT. HERMAN G. MAUL

Painful bone and joint involvements occurring in some cases of yaws were seen in the barrios of Las Piñas and Parañaque, Philippine Islands. Through the courtesies of Drs. Luis Guerrero, E. Domingo, and M. Argüelles, arrangements were perfected by which a group of one hundred cases of yaws was collected for study. The diagnoses of these cases were made by the histories, by clinical symptoms and manifestations, and by the demonstration of *Treponema pertenue* under the dark-field microscope in the cases where an open lesion was present and by a careful history of those without open lesions, so as to remove any doubt as to the diagnosis. Twenty per cent of the cases of this group of patients, as they presented themselves for treatment, suffered from bone and joint lesions. These patients were persuaded to come to the Department Hospital, Manila, for X-ray pictures and treatment. A rœntgenological survey of all the bones of the body was made of each case, regardless of whether or not the patient complained of pain in the part X-rayed. Subsequent X-ray pictures were made in order to follow the progress of the lesions under treatment. In the majority of cases the lesions show as rarefied areas, irregularly oval or elliptical in shape, with the long axis parallel to that of the bone in which the lesions are located. The size varies from

the smallest discernible area to one which is 2 or 3 centimeters in length. The rarefication presents moderately well-defined borders separating it from the unaffected bone and varies in translucency from the slightest differentiation of unnatural transparency to one simulating a perforation. Most of the lesions appear to originate in the interior of the bone, while a number can be seen as small excavations on its outer surface. When the lesion is on the surface of the bone, the periosteum is usually destroyed, but occasionally the cortex shows thickening and the periosteum is separated from the bone. In two cases of this series there is a general thinning of the cortex of the bone and a loss of the cancellous-tissue appearance. About 2 per cent of the cases show a nodular type of lesion, evidenced by swelling over the surface of the bone, with a localized thickening of the cortex, which sooner or later in the course of the disease shows rarefication in its center. In the chronic lesions marked irregularity of the bony outline is evident, and the picture characteristic of the earlier lesions is more or less lost. The bone, as a whole, becomes deformed, and the growth of the bone is interfered with both in length and breadth. This dwarflike picture is most frequently noticed in the cases showing the lesions in the epiphyses. Within the joints the destruction is most frequently seen on the parts of the articular surfaces most exposed to trauma as oval or irregularly shaped excavations, making the outline of the articular surface rough and uneven. It is concluded from this series of cases that the joint pains complained of are due, in most part, to the presence of the lesions on the articular surfaces. With the exception of the 2 per cent of cases showing as a swelling over the surface of the bone, the X-ray picture is different from the bone lesion of syphilis, in that the periosteal proliferation and the thickening of the cortex of the bone are absent. Also, in the 2 per cent of cases where thickening of the cortex is present, the thickening remains localized, does not tend to extend along the whole length of the bone, and sooner or later shows rarefication in the center of the lesion. The bone lesion of yaws may simulate (1) tuberculous or septic central abscess, (2) gumma, (3) hydatid cyst, (4) benign cyst, (5) fibrous osteitis, (6) enchondroma, (7) endothelioma, (8) secondary carcinoma, (9) myeloma, and (10) sarcoma. The differential diagnosis can be made only by combining the radiographic appearances with all clinical data, including the history, physical signs, and evidence of disease or tumor in other parts of the body. The Castellani treatment causes a gradual disap-

pearance of the bone and joint lesions. Salvarsan is a specific in these cases, and rapid regeneration of bone follows its use. Regeneration of the bone is complete at the site of the lesion if the destruction has not been too great.

Dr. Ricardo Fernandez corroborated Doctor Maul's findings and exhibited an X-ray plate of a case with lesions of yaws in the vertebræ.

R. B. GIBSON,
Editor of the Proceedings,
Manila Medical Society.